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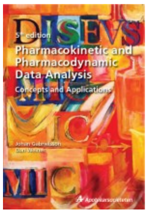
PML School: PD26 Dose-Response Time Analysis



Note: The exercise is based on exercise PD26 in the text: Gabrielsson, J. & Weiner, D.L. (5th ed., 2016). *Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications*. Swedish Pharmaceutical Press, Stockholm.

PD26: Problem specification

- New potent antibacterial compound was being developed
- A 10,000 unit dose of a resistant bacterial strain was injected into blood stream of four groups of Wistar rats
- A dose of 1, 2, 4 or 8 µg of antibiotic was given to each of the groups
- Blood was drawn at selected time points for bacterial count

Gabrielsson & Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications, 5th Edition, Swedish Pharmacology Press (2015)

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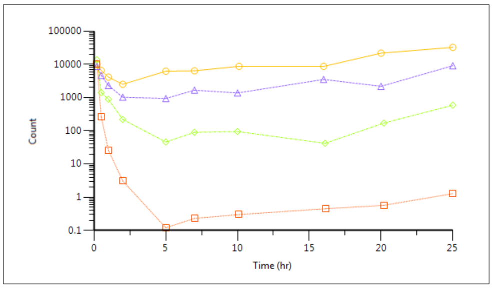
PD26: Exploratory Data Analysis

Plot of response versus time



Gabrielsson & Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications, 5th Edition, Swedish Pharmacology Press (2015)

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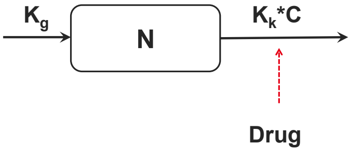
PD26: Turnover model with stimulation of loss



K_g – growth rate

K_k – bacterial kill rate

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PD26: Model Equations + Textual Model (simple)

$D = Dose \cdot e^{-K_e \cdot t}$ — 1st order elimination of IV bolus dose

$\frac{dN}{dt} = K_g \cdot N - K_k \cdot D \cdot N$ — Turnover Model with linear Stimulation of Loss

```
test(){
    covariate(dose grp)                   # taking amount of dose from input
                                          # 1st order elimination of amount of dose
                                          # Turnover model
    sequence{N = 10000}                   # initialization of bacterial growth
    error(NEps = 1)                       # initial estimate of residual error
    observe(NObs = N + N*NEps)            # additive residual error model
    fixef(Ke = c(, 1, ))                  # initial estimate of elimination rate constant
    fixef(K1 = c(, 0.2, ))                # ditto for growth rate constant
    fixef(Kout = c(, 1, ))                # ditto for kill rate constant
}
```


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PD26: Initial Estimates

- K_g – obtained from upswing arm of the curve:
  - $K_g = \frac{\ln(\frac{N_{i+1}}{N_i})}{t_{i+1} - t_i}$
- K_k – obtained from downswing arm of the curve
  - $\frac{dN}{dt} = -K_k \cdot D \cdot N$
  - Analytical solution:
    - $N = N_0 \cdot e^{-K_k \cdot AUC_0{}^t}$
    - $K_k = \frac{\ln(\frac{N_0}{N_n})}{AUC_0{}^n}$
- K_e – initially set to 1

Gabrielsson & Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications, 5th Edition, Swedish Pharmacology Press (2015)

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PD26: Multiple Dose Simulation

$D_n{}^{\tau} = Dose \cdot e^{-K_e \cdot \tau} + Dose \cdot (e^{-K_e \cdot \tau})^2 + \cdots$ Accumulation Series

$D = Dose \cdot \frac{e^{N \cdot -K_e \cdot \tau}}{e^{-K_e \cdot \tau}} e^{-K_e \cdot t}$ General equation to calculate concentration after multiple doses

```
test(){
    covariate(dose_grp)
    tau = 24
    ndoses = 3
    sequence{
            N = 10000
    }
    # Simulation of multiple doses
    Ndose = floor(t/tau+1) < ndoses ? floor(t/tau+1) : ndoses          # actual number of doses
    md time = t - tau * (Ndose - 1)                                    # actual time after multiple doses
                                                                        #PK prediction
    secondary(accum_factor = 1 /( 1- exp(-Ke*tau)))                    # accumulation factor
    deriv(N = K1 * N - D * Kout * N)                      # Turnover model
    error(NEps = 0.1)                                     # initial estimate of residual error
    observe(NObs = N + N*NEps)                            # additive residual error model
    fixef(Ke = c(, 0.552466, ))                           # initial estimate of elimination rate constant
    fixef(K1 = c(, 0.101837, ))                           # ditto for growth rate constant
    fixef(Kout = c(, 0.824477, ))                         # ditto for kill rate constant
}
```

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Demo 1

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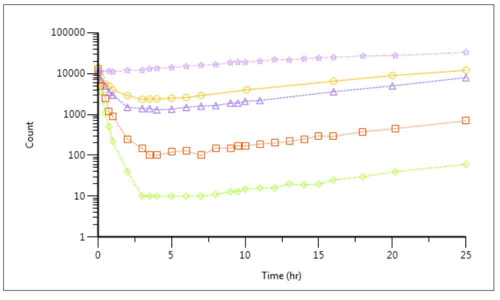
PD26: Exploratory Data Analysis (extended)

Plot of response versus time



Gabrielsson & Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications, 5th Edition, Swedish Pharmacology Press (2015)

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PD26: Model Equations + Textual Model (baseline)

$D = Dose \cdot e^{-K_e \cdot t}$ 1st order elimination of IV bolus dose

$\frac{dN}{dt} = K_g \cdot N \cdot \left(1 - \frac{N}{N_{max}}\right) - K_k \cdot D \cdot N$ Turnover Model with linear Stimulation of Loss and Baseline Growth

```
test(){
    covariate(dose_grp)                       # taking amount of dose from input
    D = dose_grp*exp(-Ke*t)                   # 1st order elimination of amount of dose
                                                   # Turnover model
    sequence{N = 10000}                       # initialization of bacterial growth
    error(NEps = 1)                           # initial estimate of residual error
    observe(NObs = N + N * NEps)              # multiplicative residual error model
    fixef(Ke = c(, 1, ))                      # initial estimate of elimination rate constant
    fixef(Kg = c(, 0.2, ))                    # ditto for growth rate constant
    fixef(Kk = c(, 1, ))                      # ditto for kill rate constant
    fixef(Nmax = c(, 33000, ))                # ditto for max baseline
}
```

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Demo 2

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PD26: Summary

- Build Turnover Model
  - Simulated PK profile
  - Turned PK model into PKPD model with frozen PK parameters
  - Fitted the model and examined results

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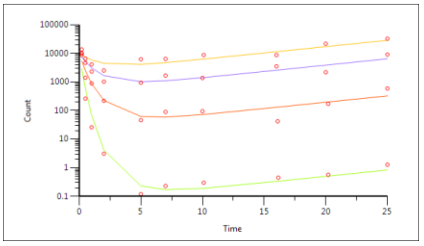
PD26: Results for simple model



	Scenario	RetCode	LogLik	-2LL	AIC	BIC	nParm	nObs	nSub	EpsShrinkage	Condition
1		1	-275.38362	550.76724	558.76724	565.52276	4	40	4	0	13.63502

	Scenario	Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI	Var. Inf. factor
1		Ke	0.552462		0.05180251	9.3766647	0.44740093	0.65752307	0.0075293
2		Kg	0.101837	1/hr	0.011857909	11.644008	0.077787885	0.12588612	0.00039452
3		Kk	0.824472		0.066275938	8.0385918	0.69005726	0.95888674	0.012324
4		stdev0	0.597		0.066746535	11.180324	0.46163084	0.73236916	

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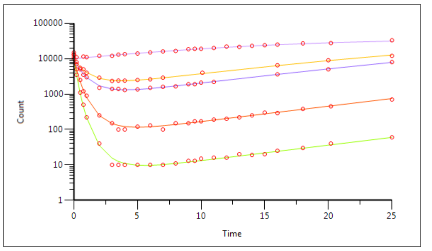
PD26: Results for baseline model



	Scenario	RetCode	LogLik	-2LL	AIC	BIC	nParm	nObs	nSub	EpsShrinkage	Condition
1		1	-660.81636	1321.6327	1331.6327	1345.1351	5	110	5	0	3133558.9

	Scenario	Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI	Var. Inf. factor
1		Ke	0.723781		0.023789073	3.2867778	0.67661183	0.77095017	0.016523
2		Kg	0.101133	1/hr	0.0027763105	2.7452073	0.095628109	0.10663789	0.0005616
3		Kk	0.921664		0.025755194	2.7944233	0.87059639	0.97273161	0.019165
4		Nmax	38699.4		2672.7514	6.9064414	33399.847	43998.953	6.9458E+08
5		stdev0	0.0956318		0.00650323	6.8002798	0.082737143	0.10852646	

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Questions?

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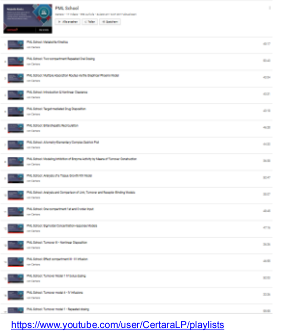
PML School: Materials

Forum: >30 Topics

https://support.certara.com/forums/forum/34-pml-school/

Youtube: 18 videos



https://www.youtube.com/user/CertaraLP/playlists

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Coming up…

2017

Transduction Modeling: Assessment of Number of Transit Compartments
Analyze a transduction rate limited response time course
August 10, 2017 | 10am EST
Presenter: Bernd Wendt

August	summer break
September	summer break
October	2 Webinars
November	2 Webinars
December	2 webinars

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Coming up…

- User Presentations
  - You are asked to present your own PML Code/Phoenix Model
  - Please send me your suggested models or ideas to
    - bernd.wendt@certara.com
  - We can discuss and eventually further refine models for live presentation at the PML School
- New Topic: NONMEM to PML Comparisons
  - Popular Models using NONMEM software
    - 1:1 translation into Phoenix Modeling Language
    - Setup and run NONMEM models in Phoenix
    - Setup and Run same model in Phoenix NLME
    - Compare Results

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